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| EXAMINER | |
|---|---|
| LI, QIAN J | |

| ART UNIT | PAPER NUMBER |
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| 1632 | |

DATE MAILED: 10/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/205,096 | Applicant(s) DRACHMAN, DANIEL B. | |
|---|---|---|---|
| | Examiner Janice Li | Art Unit 1632 | |

*-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4,5,9-12,14,19,22,28,31,35 and 41-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,9-12,14,19,28,31,35 and 41-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

## DETAILED ACTION

The Brief on Appeal filed on July 15, 2002 has been entered as Paper # 24. Please note that the examiner assigned to examine the application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1632.

Upon further search and consideration and in view of the issues presented in the Appeal Brief, PROSECUTION IS HEREBY REOPENED. New grounds of rejections set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Applicant's arguments in the Appeal Brief will only be considered or addressed to the extent that they apply to the *new grounds of rejections*; unless otherwise indicated, arguments directed to rejections that have been rendered moot in view of the new grounds of rejections will not be further addressed.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 54-57, 60-63, and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are directed to a signal sequence that is functionally located or connected to all or a portion of an auto-antigen. Given the broadest reasonable

interpretation, the claims embrace numerous structures which are functionally located or connected to all or a portion of an auto-antigen with respect to facilitate endosomal processing of antigen. However, the specification fails to provide an adequate disclosure for the broadly claimed genus.

The specification fails to define the term, and the working example discloses a nucleic acid sequence encoding AchR directly linked with a LAMP1 sequence. The specification fail to provide teachings regarding other ways of functionally connecting or locating an antigen and a signal sequence. The specification fails to provide an adequate description to teach the structures, the identifying characteristics for the claim language, considering all possible *structures* that may exist using modern biochemical and molecular biological techniques to functionally connect the two elements, one skilled in the art could not readily envision what structures the claim embrace or exclude, accordingly, the specification does not provide a reasonable guide for those seeking to practice the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of *all* or representative species of chemical structures that are "functionally connected" or "functionally located". Therefore, only the described structure meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 42, 54-57, 60-63, and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are drawn to a structure that could functionally connect a signal sequence and an antigen, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the broad class of structures encompassed by the claims. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, direct linkage alone is insufficient to describe the genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures encompassed by these claims, thus except the illustrated embodiment, one would not know how to use the invention without first carrying out undue experimentation to determine which of the structures would have the recited function. Therefore, in view of the limited guidance, the lack of predictability of

the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 41-53 and 65 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for suppressing AchR-specific T cells *in vitro* by transferring into antigen presenting cells a polynucleotide encoding the extracellular domain of AchR α-subunit, a signal sequence LAMP-1, and further exposing to apoptotic associated surface molecules FasL, Anti-FasIg, and CTLA4Ig and co-culturing said APCs with activated T cells, does not reasonably provide enablement for ablation of autoreactive T cells in *any* and *all* auto-immune disease patients using *any* and *all* antigen-presenting cells, *any* and *all* viral vectors, *any* and *all* signal sequences, *any* and *all* auto-antigens; and it does not reasonably provide enablement for selective ablation of auto-antigen-specific T cells in an auto-immune disease patient using *any* and *all* T cell detrimental products. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction

provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art, and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Claim 1 recites "a method of ablating auto-antigen-specific T cells in an auto-immune disease patients". Given the broadest reasonable interpretation in light of the specification, the claims read on a therapeutic method. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A method of ablating auto-antigen-specific T cells in an auto-immune disease patients" is defined as a method for therapeutic use, to prevent, alleviate, treat, or cure a disease within the animal to which the substance is administered, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for any and all autoimmune diseases, therefore, the claims will be evaluated by that standard.

The instant invention claims methods of treating patients suffering with an autoimmune disorder. The applicant intends accomplishing this treatment by introducing a gene encoding the entire auto-antigen or portion of the auto-antigen, introduced ex-vivo, and re-introducing the cells in vivo so as to activate the auto-antigen-specific T cells, followed by administration of a product detrimental to the activated T cells.

Previous Office actions cited Okin et al, Verma et al, and Crystal et al indicating gene therapy art in general is still in its infancy and highly unpredictable. Therefore, the general teachings in the instant specification illustrated by *in vitro* experimentation are not sufficient to support the broad claims.

In Paper #24, the applicant argues that the generic evidence regarding gene therapy provided by the Patent Office is not relevant to the claimed method which employs antigen-presenting cells (Issue III). The arguments have been carefully considered but found not persuasive for reasons of record advanced in Papers #10, 13, 15, and 17. In addition to maintain the position with respect to the generic teachings, a further analysis correlating the present disclosure relative to the scope of the claims appears below.

The specification teaches construction of a chimeric gene encoding extracellular domain of the α-subunit of AchR linked to a LAMP-1 signal sequence, and transfecting B lymphocytes with the construct. when co-culturing the transduced APCs (B cell line) with B cells transfected with CTLAIg, lymphoproliferation was significantly reduced (fig. 3). Further, killing of AchR-specific T cells was observed when applying FasL or antibody to Fas to the cell culture having the transduced B cells. In the Declarations filed after filing (Appendix 17 and 18), another experiment was done using a vaccinia vector (VVV) encoding AchR, FasL, and a truncated FADD to transfect splenocytes (APCs), which showed similar effect in cell culture as did using CTLAIg. With regard to the *in vitro* evidence disclosed, it is the general knowledge in the pertinent art, that cell culture system is a simplified model for biological study. Under an *in vivo* environment,

multiple factors act in concert, thus, the overall effect *in vivo* usually could not be predicted from the *in vitro* data. The court has made it very clear, "COURT ERRED IN ACCEPTING IN VITRO DATA AS SUPPORT FOR CLAIMS CONTAINING IN VIVO LIMITATION". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In Appendix 18, an *in vivo* study was conducted in a line of transgenic mice whose T cells express a HA-specific receptor. After intraperitoneally injection of dendritic cells transfected with a VVV-HA-FasL-FADD, or a VVV-FasL-FADD (control), the percentage of T cells expressing HA-receptors was significantly decreased in the VVV-HA-FasL-FADD group compared to the VVV-FasL-FADD group in a period of 8 days. However, the specification and/or the Declarations fail to teach whether HA-receptor bearing T cells are representative of HA activated T cells, whether such significant T cell killing effect could be observed in a mouse without a T cell HA-receptor, and in a period beyond 8 days, using any route of administration, any antigen presenting cells, any auto-antigen, linked to any signal sequence, with any viral vectors, and whether a selective killing of antigen-activated T cells could be achieved with any T cells detrimental products, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

With regard to the *in vivo* evidence provided in Appendix 18, the transgenic mice study is not sufficient to support the scope of the claims, partly because the T cells of the mouse used in the study bear specific HA-receptors, which receptors promoted targeting of administered APCs to these cells, thus, facilitated the FasL cell-killing effect. Whereas, in an auto-immune patient, such targeting mechanism is absent, therefore,

the effect of intraperitoneal or intravenously injection of transduced APCs in the patient is unpredictable. As recited previously, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Verma et al* (Sept. 1997, Nature, Vol. 389, pages 239-242) review vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of *Verma* indicate a resolution to vector targeting has not been achieved in the art (see entire article). *Crystal* (1995, Science, Vol. 270, page 404-410) also teach "AMONG THE DESIGN HURDLES FOR ALL VECTORS ARE THE NEED TO INCREASE THE EFFICIENCY OF GENE TRANSFER, TO INCREASE TARGET SPECIFICITY AND TO ENABLE THE TRANSFERRED GENE TO BE REGULATED" (page 409). Even though the VVV-HA-FasL-FADD vector was used to transfect APCs *ex vivo*, the transfected cells still face issues of targeting and proper functioning once applied *in vivo*. *Verma et al* teach, "OUR GROUP HAS USED IT TO INFECT MOUSE PRIMARY FIBROBLASTS OR MYOBLASTS WITH RETROVIRAL VECTORS PRODUCING THE FACTOR IX PROTEIN. BUT WITHIN FIVE TO SEVEN DAYS OF TRANSPLANTING THE INFECTED CELLS BACK INTO MICE, EXPRESSION OF FACTOR IX IS SHUT OFF. THIS TRANSCRIPTIONAL SHUT-OFF HAS EVEN BEEN OBSERVED IN MICE LACKING A FUNCTIONAL IMMUNE SYSTEM (NUDE MICE), AND IT CANNOT BE DUE TO CELL LOSS OR GENE DELETION BECAUSE THE TRANSPLANTED CELLS CAN BE RECOVERED". (paragraph bridging left and middle columns of page 240). *Crystal et al.* particularly

pointed out different strategies by which gene transfer is carried out and stated that the choice of an *ex-vivo* or *in vivo* strategy and of the vector is dictated by the clinical target. (See page 404, paragraph 3). *Crystal et al.* teach that there is a significant variation that exists in the genetically marked cells recovered from recipients in *ex vivo* studies, emphasizing the unpredictability in the art. (See page 405, col. 3, paragraph 3). *Crystal et al.* explicitly states that results even in *ex vivo* methods are inconsistent. (See page 409, col. 1 lines 41-43).

The transgenic mice study is not sufficient to support the scope of the claims, also because the Declaration fails to teach whether the HA-receptor bearing T cells of the transgenic mouse are representative of HA-specific activated T cells. The killing effect in the transgenic animal was associated with the presence of FasL, which receptor may be present in even non-activated T cells. Such non-activation-specific targeting effect may be seen in the control group of the transgenic mouse study on day 5 and 8 after the administration of tranfected APCs, wherein even absent of a specific (HA) antigen, the percentage of HA-receptor bearing T cells decreased (results in Table 1 of Appendix 18).

The unpredictability of the art may also be seen in the instant transgenic mouse study (Appendix 18). For example, the preamble of claim 1 calls for removal of auto-antigen-specific T cells, although on day 2 after transduced APCs administration, HA-receptor bearing T cells are significantly decreased to 10% of original, they recovered to 50% of the original on day 8, thus, the ablation of antigen-specific T cells has not been sufficiently enabled even in these transgenic mice.

The claims embrace using any antigen presenting cells, whereas dendritic cells from bone marrow are most commonly used as in the art, the claims embrace any and all types of antigen presenting cells, such as dendritic cells in dermis, keratinocytes in the epidermis, B lymphocytes, and langerhans' cells, therefore, contrary to the assertion in Issue II-b of Paper #24, the applicant fails to teach how to prepare sufficient amount of these antigen presenting cells to be used in the claimed invention.

The claims embrace any auto-antigen and any type of autoimmune diseases, a short list of them are provided in the specification (page 3, lines 14-16). The mechnisms leading to these diseases vary and cover almost every step of cellular and humoral immune responses, from various auto-antibodies to complements, to subtypes of T cells. Unlike *myasthenia gravis* (MG), the mechanism of many of these diseases are still unknown, and possibly caused by combined effect of genetic and environmental factors. Therefore, it is unpredictable if the instantly claimed method would be suitable for use in any type of autoimmune disease. Moreover, not every auto-antigen known in the art could be used in the suppression of an unwanted immune response. This is because certain antigen epitopes induce suppressive T cells that inhibit autoimmune state while others induce helper T cells accelerating the autoimmune state. *Von Herrath et al* (Ann Med 2000 Jul;32:285-92) teach, "AUTOIMMUNE PROCESSES INVOLVE AT LEAST TWO COMPONENTS THAT COEXIST IN A DELICATE EQUILIBRIUM, WHICH CAN BE CHANGED BY IMMUNIZATION. ONE COMPONENT IS AUTOAGGRESSIVE..., THE OTHER COMPONENT IS DIRECTED TO THE SAME (OR TO OTHER) SELF-ANTIGENS AND IS REGULATORY... ONLY IF THE AGGRESSIVE COMPONENT IS NOT APPROPRIATELY COUNTERBALANCED BY THE REGULATORY ONE, WILL DESTRUCTION AND DISEASE OCCUR" (Introduction, page 285). Thus, contrary to the assertion in Issue II-a of Paper

#24, the disclosure of the specification fails to provide sufficient guidance commensurate with the scope of the claims.

The claims embrace using any signal sequence linked to any auto-antigen. However, not every signal sequence is able to aid antigen presentation for every antigen. For example, *Chaux et al* (US 6,426,217) teach, "FUSION PROTEINS OF MAGE-3 AND HUMAN INVARIANT CHAIN LI, BUT NOT LAMP-1, ARE EFFICIENTLY TARGETED TO THE HLA CLASS II PEPTIDE PRESENTATION PATHWAY" (column 11, lines 25-35). Therefore, it is highly unpredictable for the antigen-presenting effect from fusions of any and all types of auto-antigens with any and all types of signal sequences.

The claims embrace any virus as carriers for claimed *ex vivo* gene therapy. *Makrides et al* teach (Protein Exp Pur. 1999; 17:183-202) "EFFICIENT EXPRESSION OF GENES IN MAMMALIAN CELLS DEPENDS ON MANY FACTORS, INCLUDING BOTH TRANSCRIPTIONAL AND TRANSPLATIONAL CONTROL ELEMENTS, RNA PROCESSING, GENE COPY NUMBER, MRNA STABILITY, THE CHROMOSOMAL SIT OF GENE INTEGRATION, POTENTIAL TOXICITY OF RECOMBINANT PROTEINS TO THE HOST CELL, AS WELL AS THE GENETIC PROPERTIES OF THE HOST." (page 183, left column). *Robbins et al* (Pharmcol Ther 1998;80:35-47) teach that each type of vector system has its unique advantages and limitations, "RETROVIAL VECTORS CAN PERMANENTLY INTEGRATE INTO THE GENOME OF THE INFECTED CELL, BUT REQUIRE MITOTIC CELL DIVISION FOR TRANSDUCTION. ADENOVIRAL VECTORS CAN EFFICIENTLY DELIVER GENES TO A WIDE VARIETY OF DIVIDING AND NONDIVIDING CELL TYPES, BUT IMMUNE ELIMINATION OF INFECTED CELLS OFTEN LIMITS GENE EXPRESSION IN VIVO. HERPES SIMPLEX VIRUS CAN DELIVER LARGE AMOUNTS OF EXOGENOUS DNA; HOWEVER, CYTOTOXICITY AND MAINTENANCE OF TRANSGENE EXPRESSION REMAIN AS OBSTACLES. AAV ALSO INFECTS MANY NONDIVIDING AND DIVIDING CELL TYPES, BUT HAS LIMITED DNA CAPACITY"

(abstract). For *in vivo* gene therapy in an auto-immune patient, these are the factors have to be considered.

Claims also embrace any and all products detrimental to activated T cell proliferation. The specification teaches CTLA4Ig, FasL, antibodies to Fas, and antibodies to B7 molecules as illustrative products. However, the art-known detrimental products to activated T cells are far more beyond the illustrative embodiment, such as antibodies to any of the many T cell surface markers, immune suppressive drugs, etc. Whether these molecules could be as effective as the illustrated embodiment is unpredictable. Cyclosporine A is a commonly used product detrimental to activated T cells, however, the effect is not selective to autoreactive T cells. Thus, contrary to the assertion in Issue II-c of Paper #24, the specification fails to provide sufficient guidance commensurate in scope with the claims.

In Issue II-c of Paper #24, the applicant argue that the Office has not put forward any reasoning why timing would be critical or would not be within the skill of the ordinary artisan to determine without undue experimentation. The reasoning could be seen in the teachings of *Von Herrath et al*, "THE TYPE OF AUTOREACTIVE T-CELL REPERTOIRE, THE TIMING OF ANTIGEN ADMINISTRATION, AND THE CHOICE OF SELF-ANTIGEN ARE CRUCIAL FEATURES THAT MUST BE UNDERSTOOD IF AUTOIMMUNE DISEASES ARE TO BE CONTROLLED BY IMMUNIZATION (right column page 292), and in the teachings of *Kristiansen et al* (Genes and Immunity 2000;1:170-84), in summarizing the knowledge in the art long after the instant filing date, "FUTURE STRATEGIES SHOULD INCLUDE A MORE SPECIFIC APPROACH TO THE POSSIBLE INVOLVEMENT OF CTLA4 IN THE PATHOGENETICAL PROCESS, E.G. BY STUDYING THE CTLA4 EXPRESSION DURING DISEASE DEVELOPMENT-RATHER THAN STUDYING ONLY LIGAND-RECEPTOR

INTERACTION-IN THE RODENT SPONTANEOUS DISEASE MODELS" (last paragraph, page 180). This teaching implies the complicated nature of an autoimmune response as well as the dynamically changes of various factors in different stages of the disease development. In addition, the specification fails to teach the fate of the antigen presenting cells and viral vectors which express auto-antigens, whose consistent presence could either be a force to suppress antigen-specific activated T cells or a trigger to acerbate the auto-immune state depending on the delicate balance of T cell activation and inhibition, particularly in view of the fact that auto-immune patients often are susceptible to auto-antigen stimulants.

Last, but not the least, autoimmunity is caused by the loss of tolerance to self-determinants and activation of autoreactive lymphocytes, while the concept of the instant invention tackles the activation of autoreactive lymphocyte, it is unpredictable whether the method is able to ablate the autoreactive T cells in *myasthenia gravis* because the immunological state of MG patients, the constant presence of over-expressed auto-antigen in thymus, defective regulation of apoptosis, and the defects either in the number or function of CD8+ T cells (table 1, *Carrieri et al,* Ann Med 1999;31:52-6).

Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed invention. Although the instant specification provides *in vitro* and certain *in vivo* data to illustrate the claimed method, it is not enabled for its full scope because the specification fails to teach how to overcome the aforementioned difficulties in the art, the general knowledge and levels of skill in the

art do not supplement the omitted description, because specific, not general guidance is what is needed.

Accordingly determination of the effects of claimed method in autoimmune patients is not predictable until they are actually practiced, hence resulting in a trial and error situation. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *ex vivo* gene therapy for any and all autoimmune diseases, in particular for selective ablation of autoreactive T cells in a patient, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *ex vivo* gene therapy of any and all autoimmune diseases, and the breadth of the claims directed to the use of numerous therapeutic combinations of autoantigens/signal sequences/APCs/vectors/detrimental products, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

***Claim Rejections - 35 USC § 102***

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 54, 58, 59, 60, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable by *August et al* (US 5,633,234).

Claims 58-60, 64 are directed to a virus which infects human APCs and which comprises a polynucleotide encodes all or a portion of an auto-antigen and a signal sequence so that said auto-antigen could be processed by endosomes, preferably the virus is an attenuated vaccinia virus. Claim 54 is directed to the antigen presenting cells transfected with said polynucleotide.

*August et al* teach that a recombinant vaccinia virus that could be used in vaccination of an autoimmune disease (column 16, lines 21-35), wherein the virus has attenuated pathogenicity (column 6, line 57), that a recombinant vector could be made to encode an auto-antigen, such as an acetylcholine receptor in the case of myasthenia gravis linked to the endosomal/lysosomal targeting signal, and trasfecting an antigen presenting cell, such as dendritic cell for generating an immune tolerance (column 19, lines 26-54). Therefore, *August et al* anticipate instant claims.

Claims 58, 59, and 64 are rejected under 35 U.S.C. 102(e) as being anticipated by *Steinman et al* (US 6,300,090).

The claims are directed to a virus which infects human APCs and which comprises a polynucleotide encodes all or a portion of an auto-antigen, preferably the virus is an attenuated vaccinia virus.

*Steinman et al* teach that a recombinant vaccinia virus that could be used to deliver antigens to antigen presenting cells, particularly dendritic cells (column 8, line 2),

wherein the virus is attenuated (column 11, line 20), wherein the antigens include autoantigens (column 9, line 30), wherein the dendritic cells could be used in the treatment of autoimmune diseases (column 11, lines 38-39). Therefore, *Steinman et al* anticipate the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 54, 58, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over *August et al* (US 5,633,234), in view of *Attassi et al* (Cri Rev 1997;17:481-95).

*August et al* teach a virus encoding a AchR auto-antigen and antigen presenting cells transfected by the virus for use in myasthenia gravis disease. *August et al* do not particularly teach the extracellular domain of $\alpha$ -subunit of AchR.

*Attassi et al* teach that in MG disease, the extracellular portion of AchR $\alpha$ subunit serves as epitope recognized by the T and B lymphocytes (see abstract and right column in page 482).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the recombinant polynucleotide taught by *August et al,* by simply substituting the full-length AchR with the extracellular domain of $\alpha$ -

subunit of AchR as taught by *Attassi et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the virus because it is advantageous to insert a confirmed antigenic epitope having a shorter sequence and without unrelated polypeptides that may interfere with effective immune response. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 54, 55, 56, 58, 60, 61, 62, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over *August et al* (US 5,633,234) as applied to claims 54, 58, 66, and 67 above, and further in view of *Bellgrau et al* (US 5,759,536).

Claims 55, 56, 61, 62 are further directed antigen presenting cells further encoding a protein which is detrimental to activated T cell survival, preferably a FasL.

*August et al* do not teach transfecting APCs with FasL.

*Bellgrau et al* teach use of Fas Ligand to suppress T lymphocyte-mediated immune response. They teach that cells expressing an autoantigen could be further introduced to a gene expressing Fas ligand, so that suppress T lymphocyte-mediated disease (see claims 6 and 7). They go on to teach that the cells could be used in transplant rejection, in autoimmune diabetes, and *myasthenia gravis* (column 5, lines 23-40).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *August et al and Bellgrau et al,* by simply including the FasL coding region in the viral vector of *August et al*, or using

two separate transfected cells as taught by *Bellgrau et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the method because *Bellgrau et al* provide a relatively simple method for autoreactive T cell suppression. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 20, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER